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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/574,461	11/30/95	BARONE	16528X-0155-

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HM12/0319

EXAMINER  
RICIGLIANO, J

ART UNIT	PAPER NUMBER
1618	23

DATE MAILED: 03/19/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.  
**08/574,461**

Applicant(s)  
**Barone et al.**

Examiner  
**Joseph W. Ricigliano Ph. D.**

Group Art Unit  
**1618**



☒ Responsive to communication(s) filed on 9/28/98 and 11/13/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

☒ Claim(s) 1-15 and 37-39 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-15 and 37-39 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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1. **Please note:** The examiner's art unit designation has changed to 1618.

***Continued Prosecution Application***

2. The request filed on 11/13/98 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/574,461 is acceptable and a CPA has been established. An action on the CPA follows.

***Amendments Entered***

Applicants' amendment dated 9/28/98 received by OIPE 10/2/98 has been entered.

Claim 9 has been canceled and new claim 39 has been entered.

Claims 1-8, 10-15, 37-39 are pending.

***Claim Rejections - 35 USC § 112***

3. Claim 39 and its dependent claims 2-7 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have submitted new claim 39 which recites that the polymers comprise a label other than a monomer unit of the polymer. Applicants can overcome this rejection by indicating where support for the limitation in claim 39 can be found in the application as originally submitted.

4. Claims 1-8, 10-15, 37-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

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possession of the claimed invention. The two independent claims have been amended to recite measuring a property of the mixture as an indicator of the efficiency of the synthesizing step. Applicants have indicated that support for amendment can be found on page 18 of the specification. However, the specification does not appear to support measuring a property of a mixture, rather, it appears to support measuring the presence of individual components present in the mixture via a property of the components. Applicants can overcome this rejection by indicating where support for the limitation in claims 1 and 10 can be found in the application as originally submitted by page and line number.

5. Claims 1-8, 10-15, 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for measuring the presence of the individual components present in a mixture using a property of a label (i.e., the composition of the mixture) does not reasonably provide enablement for measuring a property of the mixture of diverse unbound polymers as an indicator of the efficiency of the synthesizing step. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-8, 10-15, 37-39 are directed toward a method of measuring polymer array synthesis. The disclosure teaches the synthesis and addition of a label to each member of a polymer array, subsequent cleavage of the array and analysis of the resulting mixture of polymers wherein the individual members of the array are detected by a property of the label added. However, the measurement of a property of the mixture itself as a measure of synthesis step

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efficiency does not appear to be within the scope of reasonable experimentation. The factors to be considered in a determination of undue experimentation are disclosed in *In re Wands*, (U.S.P.Q. 2d 1400 (CAFC 1988)). The factors to be considered include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of the claims.

Contrary to applicants assertions on page 5 of the 9/28/98 response the specification at page 18 does not support such methods and a number of factors would prevent one of skill in the art from practicing the invention without undue experimentation, these are summarized as follows:

- 1) The specification fails to give adequate direction and guidance to which properties of the mixture as a whole would be useful as a measure of synthetic efficiency.
- 2) Applicants have failed to provide any working examples where a property of the mixture as a whole is used to determine synthetic efficiency.
- 3) The breadth of the claims encompasses a large number of potential properties from vapor pressure measurements to conductivity.
- 4) The state of the prior art is such that the efficiency of array synthesis has been monitored by monitoring the composition of the population released from the supports (see 103 (a) rejection over Lam et al) not a property of the mixture itself
- 5) The art is inherently unpredictable because it is unclear how individual members will contribute to the bulk properties of the mixture. For example, an individual member of a population may

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strongly influence the conductivity of the mixture in a manner which is disproportionate to the efficiency of monomer incorporation.

Therefore, while it is true that the level of skill in the art is high, it would require undue experimentation to make and use the invention commensurate in scope with that claimed in the absence of explicit guidance as to which properties of the mixture are useful as indicators of synthetic efficiency and how to interpret them as set forth above.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-7, 10, 12-15, 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1-7, 10, 12-15, 37-39 recite synthesizing a preselected array of diverse polymers.

This is vague and indefinite because it is unclear if applicant is intending to encompass in the claim

31 17198 *an array having* more than one type of polymer "backbone" (e.g., polyamides and nucleotides) or if by "diverse" applicant meant that the sequence of the monomers is different but only one type of "backbone" is present. Therefore it is not possible to determine the metes and bounds of the invention as claimed.

9. Claim 3 -5 recite the polymer are heterogeneous by size. This is vague and indefinite because it is unclear what "size" is meant to refer to. Does applicant intend size to be the number of monomeric units in the polymer, the mass, a measurement of length in some dimension or a

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measurement of volume? Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

✓ 10. Claim 2 recites the polymer comprises a single isomer. This is vague and indefinite because isomers are compounds that share the same number of atoms of each element they contain but differ in structural arrangement. Hence, <sup>it</sup> is unclear if applicant intends all of the polymers in the array to be comprised of the same number of atoms of each element contained or if each of the labeled polymers must be comprised of one isomeric monomer or if a portion of a monomer which is isomeric is sufficient to meet the limitation of the claim. Moreover, it is unclear which type of "isomer" applicant is referring to structural, enantiomeric, diastereomeric....

Therefore, it is not possible to determine the metes and bounds of the invention as claimed. It is noted that in the case of structural isomers as opposed to stereochemical isomers the labels could have divergent properties which may raise significant issues under 112 first paragraph.

11. Claim 15 recites that the label is a single isomer. This is vague and indefinite because it is unclear if applicant is referring to structural isomers or stereochemical isomers. Therefore it is not possible to determine the metes and bounds of the invention as claimed. It is noted that in the case of structural isomers as opposed to stereochemical isomers the labels could have divergent properties which may raise significant issues under 112 first paragraph.

12. Claim 39 and its dependent claims 2-7 and 37 recite that the polymers comprise a label other than the monomer unit of the polymers. This is vague and indefinite because it is unclear how to interpret labels that form when a polymer is formed from monomer subunits when the monomers themselves do not contain the "label" per se (e.g. the "backbone" of the polymer

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becomes a chromophore itself). Moreover, it is unclear if this claim language is intended to exclude labels where only a portion of the monomer unit, (e.g., the indole of tryptophan) is a UV and fluorescent label but does not constitute a monomer of a peptide in and of itself. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

***Claim Rejections - 35 USC § 103***

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-8, 10-15 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al [5,640,489; 102(e) date of at least 7/2/91] in view of Fodor et al [Science 251: 767 (1991)] and applicants' disclosure of the prior art teachings.

With respect to independent claims 1 and 10: Lam et al teach the synthesis of random bio-oligomers ( which reads on diverse polymers, see abstract) which may be peptides or oligonucleotides or a peptide oligonucleotide chimera (col. 5, lines 8-17). Lam et al teach the synthesis of the oligomers using the split and combine method whereby individual beads are used to synthesize one polymer per bead (figure 1). Lam et al teach synthesizing arrays of polymers using different protocols in order to compare the results of the synthetic process on the array produced. Lam et al also teach separately cleaving the collections of polymers from the support



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beads to form separate mixtures and measuring the components present via a property (UV absorbance in this instance) in order to examine the products produced using similar synthesis protocols. Lam et al specifically note that the incorporation of individual components such as valine are different between the methods employed which reads on measuring a "property" (the composition) of the mixture of unbound polymers as an indicator of the efficiency of the synthesizing step (see figure 3 and col. 34, line 60 - col. 35, line 55). In that the array of polymers produced in one method is compared to the array produced in the second method one array reads on a reference array.

With respect to the dependent claims, Lam et al specifically recites the oligomers of the array can be oligonucleotides as required in claims 8 and 11 (col. 5, lines 8-17). Lam et al teach that the use of cleavable linkers, as required by claim 13, are well known in the art (col. 16, lines 10-40). In that the peptides exemplified by Lam et al were detected by their absorbance at 215 nm (see figure 3 left axis) they clearly are comprised of a detectable label as defined by applicant on page 12 of the specification and required in claim 14. In that the 215nm absorbance by the exemplified peptides in Figure 3 is due to the amide bonds of the backbone the polymers comprise a label other than a monomer unit as required by claim 39. [That the absorbance at 215 nm is due to the amide backbone is well known in the art. However, the examiner has attached pages 161-162 of *Spectrophotometric identification of Organic Compounds (2nd ed, 1967)* for applicants convenience which clearly evidences this assertion.]. Additionally, it is noted that the indole ring of tryptophan can serve as a detectable label at 280 nm (see Lam et al col. 33, lines 55-57) and that the indole ring itself does not comprise a monomer. Therefore, Lam et al additionally reads

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on instant claim 39. In that the backbone amide chromophore comprises a single isomer and alternatively the indole of tryptophan comprises a single isomer (which is fluorescent) Lam et al reads on claims 14, 15 and 38. In that each of the peptides in the exemplified arrays contain a tryptophan they comprise a single isomer as required by claim 2. In addition, since different peptides with different compositions and masses are present, they are heterogeneous by "size." In that Lam et al teach the use of reverse phase HPLC to monitor the composition of the oligomer mixtures cleaved from the array, Lam et al render obvious the use of other well-known HPLC methods, which in view of applicants' disclosure of prior art teachings are notoriously well known and established in the art (see pages 38 and 39 of the specification). In addition, the analyses of mixtures of materials by gel electrophoresis as required in claim 5, especially the analysis of peptides and nucleotides is notoriously well known in the art as clearly evidenced by applicants' reliance on standard texts, laboratory manuals and manufacturers' literature, see page 38 and 39 of the specification.

Lam et al do not teach the formation of arrays on planer surfaces, where each member of the polymer set occupies a different region of the substrate.

Fodor et al teach the synthesis of polymer arrays on planar substrates where each member of the polymer array occupies a different region of the substrate.

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to monitor the synthesis of polymer arrays synthesized on a planer support as taught by Fodor using a method of analysis as taught by Lam et al, because Lam et al teach the desirability of monitoring polymer array synthesis in order to compare the methods utilized in the

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synthetic process (see example 7 "*Comparison of the claimed method with the conventional method of peptide synthesis*" starting in column 7 at line 60) which is applicable to arrays synthesized on any support(s). One of ordinary skill in the art would have been motivated to do so in order to compare array synthesis protocols and optimize array synthesis (which is desirable whether the array has been prepared on a planar support or spherical supports, segmental supports, fiber supports... ~~as are~~ each are known in the art) as taught by Lam et al (*loc cit*). One *of Lam* 7/1 7/95 ordinary skill in the art would reasonably have expected to be successful because the basic method of preparing an array of oligomers on supports, cleaving them to form a mixture of oligomers and analyzing them had already been conducted by Lam et al. One of ordinary skill in the art would also have reasonably expected the use of gel electrophoresis, and HPLC chromatography to be successful because these are notoriously well known methods of analysis which have been applied to oligomeric compounds such as peptides and nucleotides.

15. Claims 1-8, 10-15 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al [5,640,489; 102(e) date of at least 7/2/91] in view of Holmes [US 5,679,773] and applicants' disclosure of the prior art teachings.

See the teachings of Lam et al and applicants' disclosure of the prior art teaching as applied to claims 1-8, 10-15 and 37-39 under 35 USC 103(a) as being unpatentable over Lam et al in view of Fodor and applicants disclosure of the teachings of the prior art, *supra*.

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Holmes et al teach the synthesis of polymer arrays on planar substrates where each member of the polymer array occupies a different region of the substrate and the desirability of determining the fidelity of synthesis of such arrays (column 19, lines 33-58).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to monitor the synthesis of polymer arrays synthesized on a planer support as taught by Holmes using a method of analysis as taught by Lam et al, because Lam et al teach the desirability of monitoring polymer array synthesis in order to compare the methods utilized in the synthetic process (see example 7 "*Comparison of the claimed method with the conventional method of peptide synthesis*" starting in column 7 at line 60) which analyze mixtures of polymers cleaved from the support and Holmes teaches the desirability of determining the fidelity of array synthesis on planar supports by cleaving the polymers from the support. One of ordinary skill in the art would have been motivated to do so in order to compare array synthesis protocols and the resulting fidelity of array synthesis as suggested by Lam et al and Holmes. One ordinary skill in the art would reasonably have expected to be successful because the basic method of preparing an array of oligomers on supports, cleaving them to form a mixture of oligomers and analyzing them had already been conducted by Lam et al. One of ordinary skill in the art would also have reasonably expected the use of gel electrophoresis, and HPLC chromatography to be successful because these are notoriously well known methods of analysis which have been applied to oligomeric compounds such as peptides and nucleotides.

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*Response to Arguments*


16. Applicants' arguments with respect to claims 1-15, 37 and 38 have been considered but are moot in view of the new ground(s) of rejection.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can normally be reached on Monday through Thursday from 7:30 A.M. to 5:00 P.M. and alternate Fridays from 7:30 A.M. to 5:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald Adams, can be reached at (703) 308-0570.

Joseph W. Ricigliano Ph. D.

  
PONNATHAPURA ACHUTAMURTHY  
PRIMARY EXAMINER  
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